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| EXAMINER | |
|---|---|
| BRADLEY, CHRISTINA | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/552,381 | BALDWIN ET AL. | |
| | Examiner | Art Unit | |
| | CHRISTINA BRADLEY | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *41-81* is/are pending in the application.

4a) Of the above claim(s) *47-52 and 63-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-46 and 53-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election of Group I, claims 41-63, in the reply filed on 08/06/2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 64-81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

2. Applicant's election with traverse of the species bismuth subcitrate and colorectal carcinoma in the reply filed on 08/06/2010 is acknowledged. The traversal is on the ground(s) that Applicants have claimed a small number of species possibilities. This is found persuasive, in part. All bismuth species were searched and examined. However, the species desferrioxamine (DFO), ethylene diamine tetracetic acid (EDTA), diethylene triamine pentacetic acid (DTPA), elioquinol, metal ions other than bismuth, exchange-inert complexes between non-amidated gastrin and Co(III) or Cr(III) are withdrawn from consideration. The use of bismuth compounds to treat conditions that are associated with elevated levels of non-amidated gastrin is not novel over the prior art (see rejection over DeGiacomo et al. below). Therefore, unity of invention is lacking *a posteriori*. The requirement is still deemed proper and is therefore made FINAL. The election of species requirement with respect to the disease or condition is withdrawn. Claims 47-52 and 63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

3. In summary, claims 41-81 are pending; claims 47-52 and 63-81 are withdrawn and claims 41-46 and 53-62 are examined.

***Priority***

4. If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition

must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

***Information Disclosure Statement***

5. The information disclosure statement filed 10/16/2006 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because numerous non-patent literature citations are missing titles (the specific citations have been lined-through). The information referred to in these citations has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of

determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

***Sequence Compliance***

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below. Peptide sequences on at least the following pages require sequence identifiers and must be included in the sequence listing: p. 32, ln 37; p. 33, ln, 1; p. 36, lns 5, 7; p. 45, lns 22, 28, 32, 34; p. 56, lns 32, 34; p. 68, lns 11, 17; p. 69, lns 2, 6, 24 and Table 10; p. 70, ln 37; p. 71, ln 2; p. 72, lns 2, 14, 18, 19, 22; p. 73, lns 17, 18 and Table 11; p. 74, lns 7, 9, 26, 28, 36; p. 76, lns 5, 24, 30, 35; p. 79, lns 31, 33, 34; p. 80, lns 1, 14, 35; p. 81, lns 15, 24, 28, 29; and p. 82, ln 1. Correction is required. In addition, Applicant should review the entire specification for additional peptide sequences containing four or more amino acids to ensure that they are in compliance with the sequence rules.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 41-46 and 53-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains,

or with which it is most nearly connected, to make and/or use the invention. To comply with the enablement requirements of 35 U.S.C. §112, first paragraph, a specification must adequately teach how to make and how to use a claimed invention throughout its scope, without undue experimentation. *Plant Genetic Systems N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339, 65 USPQ2d 1452, 1455 (Fed. Cir. 2003). There are a variety of factors which may be considered in determining whether a disclosure would require undue experimentation. These factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

9. The invention is drawn to a method of treating a condition associated with elevated levels of non-amidated gastrin, comprising administering a compound that inhibits the binding of ferric ions to glycine-extended gastrin17, progastrin or progastrin-derived peptides and the activity of non-amidated gastrins but that does not inhibit the activity of amidated gastrin.

10. The USPTO provides claim terms with their broadest reasonable interpretations in light of the specification. The claim terms "treating" and "condition associated with elevated levels of non-amidated gastrin" are defined as follows:

11. The specification on p. 28, lns 3-17 states that "the terms 'treating', 'treatment' and the like are used herein to mean affecting a subject, tissue or cell to obtain a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing a disease or sign or symptom thereof, and/or may be therapeutic in terms of a partial

or complete cure of a disease. 'Treating' as used herein covers any treatment of, or prevention of disease in a vertebrate, a mammal, particularly a human, and includes preventing the disease from occurring in a subject who may be predisposed to the disease, but has not yet been diagnosed as having it; inhibiting the disease, ie., arresting its development; or relieving or ameliorating the effects of the disease, ie., cause regression of the effects of the disease." Therefore, the scope of the instant claims includes both inhibition and cure of a disease in a diagnosed patient and prevention of a disease in an undiagnosed patient.

12. The specification on p. 27, lns 11-15 states that "The expression "elevated non-amidated gastrin" is to be understood to mean that the blood levels, rate of secretion or activity of Ggly are significantly higher than those in a normal subject of comparable age, sex and weight." Therefore, the scope of the instant claims includes all conditions in which blood levels, rate of secretion or activity of Ggly are significantly higher than those in a normal subject of comparable age, sex and weight, whether or not said disease or condition can be attributed to the elevated non-amidated gastrin. The specification states that preferably the condition is selected from the group consisting of gastrin-producing tumours, such as colorectal carcinomas, gastrinomas, islet cell carcinomas, lung cancer, ovarian cancer, pituitary cancer and pancreatic cancer, or from other conditions in which serum gastrins are elevated, such as atrophic gastritis; G cell hyperplasia; pernicious anaemia; and renal failure; or from other conditions affecting the gastrointestinal mucosa, such as ulcerative colitis.

13. The specification does not provide a limiting structural definition of compounds that inhibit the binding of ferric ions to glycine-extended gastrin17, progastrin or progastrin-derived peptides and the activity of non-amidated gastrins but that do not inhibit the activity of amidated

gastrin but rather claims the compounds only in terms of function. Examples of the compounds are bismuth ions and complexes as well as chelators. In view of the election of species requirement, only bismuth ions and complexes are addressed here.

14. First, with respect to prevention, the art clearly does not recognize that it is possible to prevent conditions such as colorectal carcinomas, gastrinomas, islet cell carcinomas, lung cancer, ovarian cancer, pituitary cancer and pancreatic cancer with pharmaceutical treatment including bismuth ions and complexes. The specification does not provide evidence that supports the use of bismuth ions or complexes to prevent all conditions associated with elevated levels of non-amidated gastrin. Furthermore, the specification fails to provide guidance on how to identify patients who are in need of such preventative treatment.

15. Next, with respect to treatment as it is limited to arresting development of the disease, relieving or ameliorating the effects of the disease, or causing regression of the effects of the disease, the specification does not enable the practice of the method. Applicants recognize that the role of non-amidated gastrin in disease is controversial "the biological roles of Ggly are still the subject of debate" (p. 87, ln 21). Although it may be possible to identify a patient having elevated non-amidated gastrin levels by measuring blood levels, rate of secretion or activity of Ggly and comparing to those in a normal subject of comparable age, sex and weight, it is not possible to identify, based on the knowledge in the art and in the specification, which of these patients suffer from conditions that can be treated by inhibiting non-amidated gastrin. The scope of diseases and conditions covered in the claims is extensively broad yet neither the prior art or the specification has established a causal role for non-amidated gastrin in a single disease or that a single disease can be treating by disrupting the binding of ferric ions to glycine-extended

gastrin17. Even for colorectal carcinoma, to which the specification is primarily directed, the prior art is unclear: Siddheshwar et al. ("Plasma levels of progastrin but not amidated gastrin or glycine extended gastrin are elevated in patients with colorectal carcinoma" *Gut*, **2001**, *48*, 47-52) teach that "Plasma levels of progastrin, but not amidated gastrin or glycine extended gastrin, are significantly elevated in patients with colorectal cancer compared with those with colorectal polyps or controls, irrespective of their *H pylori* status." The Siddheshwar et al. study casts doubt on the role of non-amidated gastrin in colorectal cancer and therefore inhibition of it as a means for treatment. Furthermore, even for bismuth therapy, to which the specification is primarily directed and has been used extensively to treat gastrointestinal conditions, the specification states that its "broad spectrum of effects is associated with a large number of putative mechanisms of action" including antibacterial, stimulation of an influx of macrophage, and prostaglandin synthesis, inhibition of pepsin activity, and antidiarrhoeal and anti-inflammatory effects (p. 87, lns 1-18). Thus, the wide-use of bismuth therapy does not support the claimed method of treating all conditions associated with elevated non-amidated gastrin by inhibiting ferric ion binding to glycine-extended gastrin17.

16. The specification provides extensive data establishing that glycine-extended gastrin binds to ferric ions at Glu7, and that ferric ion binding is essential for biological activity. In addition, the specification presents data suggesting that bismuth ions selectively block the biological activity of Ggly. The addition of bismuth ions significantly inhibited both Ggly-stimulated inositol phosphate production (Figure 13) and proliferation (Figure 14) in the human colorectal carcinoma cell line HT29, and migration of the gastric epithelial cell line IMGE5 (Figure 15). In addition bismuth ions completely block the stimulatory effect of Ggly on rectal mucosa in the

defunctioned rat model (Figure 19). Data showing that bismuth ions also bind to Glu7 but inhibit Ggly-stimulated biological activity suggest that bismuth ions compete for the ferric ion binding site, but that the complex formed is inactive. The specification presents data suggesting that in contrast to Ggly, bismuth ions do not affect the biological activity of Gamide. The addition of bismuth ions did not significantly inhibit either Gamide- stimulated inositol phosphate production in COS-7 cells transiently transfected with the CCK-2 receptor (Figure 13) or proliferation in CHO cells stably transfected with the CCK-2 receptor (Figure 14). These observations are consistent the data showing that binding of ferric ions to Glu7 of Gamide is not required for biological activity.

17. The instant specification does not provide working examples that directly test the effect of bismuth on conditions associated with elevated glycine-extended gastrin. Rather the data in the specification establish that bismuth ions and complexes are capable of mitigating the effect of glycine-extended gastrin on proliferation and migration in gastric and colonic cell lines, and on colon carcinogenesis in rats treated with azoxymethane. It is not clear how this data generated from studies in which glycine-extended gastrin is administered to cells or animals correlates to the treatment of colorectal carcinoma given that the role of non-amidated gastrin in this disease is not well-established. The skill in the art is not advanced. As acknowledged by Applicants in the specification (p. 87, lns 26-28) "bismuth has not previously been proposed for the treatment of experimental or clinical colon cancer," and "there have not been any attempts to direct such therapies to specific inactivation of Ggly, or blockade of the interaction between Ggly and its receptor" (p. 7, lns 18-20). Furthermore, Applicants' work constitutes a novel identification of

the "essential role of a metal ion in the action of a hormone" (p. 79, lines 20-24). Therefore, in order to enable the method, the specification should provide significant guidance.

18. Although the specification states that animal models of colorectal cancer are known in the art, it would constitute undue experimentation in determining if one of the claimed bismuth ions or complexes would be effective at colorectal carcinoma because the role of non-amidated glycine in this disease has not been established. In order to practice the full scope of the claims, the skilled artisan would be burdened with determining for which diseases the inhibition of non-amidated gastrin is an effective therapeutic strategy and whether or not bismuth ions or complexes can be used as a means to inhibit non-amidated gastrin in these diseases. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation. Therefore, in view of the *Wands* factors, the claims appear to require undue experimentation to use the full scope of the claimed invention.

***Claim Rejections - 35 USC § 102***

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 41-44, 53 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by De Giacomo et al. ("*Helicobacter pylori* Infection and Chronic Gastritis: Clinical, Serological and Histological Correlations in Children Treated with Amoxicillin and Colloidal Bismuth Subcitrate," *J. Pediatric Gastroenterology and Nutrition*, **1990**, *11*, 310-316). De Giacomo et al.

teach the administration of colloidal bismuth subcitrate to patients suffering from *Helicobacter pylori* infection and chronic gastritis. The instant application states that colloidal bismuth subcitrate is a treatment having the ability to inhibit the binding of ferric ions to glycine-extended gastrin17, and that *Helicobacter pylori* infection and chronic gastritis are conditions associated with elevated levels of non-amidated gastrin, as evidenced at least by claims 45 and 54. Therefore, the prior art of DeGiacomo et al. meets all of the structural and method step limitations of claims 41-44, 53 and 62. The additional limitations regarding non-amidated gastrins are functional effects and are inherently met by the prior art.

21. Claims 41-46, 53-57 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by De Pullan et al. ("Comparison of bismuth citrate and 5-aminosalicylic acid enemas in distal ulcerative colitis: a controlled trial," *Gut*, **1993**, *34*, 676-679). Pullen et al. teach the administration of colloidal bismuth subcitrate to patients suffering from distal ulcerative colitis. The instant application states that colloidal bismuth subcitrate is a treatment having the ability to inhibit the binding of ferric ions to glycine-extended gastrin17, and that distal ulcerative colitis is a condition associated with elevated levels of non-amidated gastrin, as evidenced at least by claims 45 and 62. Therefore, the prior art of Pullan et al. meets all of the structural and method step limitations of claims 41-44, 53 and 62. The additional limitations regarding non-amidated gastrins are functional effects and are inherently met by the prior art.

***Conclusion***

22. No claims allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-

9044. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 8:30 A.M. to 4:30 P.M.

24. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

25. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

cmb